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14. ABSTRACT

This study will evaluate Constraint-Induced Movement (CI) therapy for promoting motor recovery in veterans and civilians with traumatic brain injury (TBI). This form of physical rehabilitation has been shown to substantially improve motor function after brain injury not due to trauma and to provoke a widespread neuroplastic response in the brain. This study (N = 80) is a single blind, randomized controlled trial that compares CI therapy for improving use of the more-affected arm in adults with TBI to a holistic fitness program named Lakeshore Enriched Fitness Training (LEFT). In addition to assessing changes from pre-treatment in more-affected arm motor function at post-treatment and 1-year afterwards, changes will be examined in white matter, grey matter, and functional brain activity. Products at the end of the first year of this blinded study are a manual of procedures and a method for generating synthetic neuroimaging data for the purpose of evaluating the sensitivity of the techniques proposed for quantifying changes in grey matter.

15. SUBJECT TERMS
Constraint-Induced Movement therapy, neurorehabilitation, traumatic brain injury, upper-extremity, hemiparesis, neuroplasticity

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1. INTRODUCTION

The purpose of this study is to determine the value of Constraint-Induced Movement (CI) therapy for promoting motor recovery in veterans and civilians with traumatic brain injury (TBI). CI therapy is a family of physical rehabilitation interventions derived from basic research in behavioral neuroscience and behavioral psychology. Each of the members of the family has four main components: (a) extensive, intensive training; (b) organization of the training following shaping principles, a well-known method in psychology for teaching new behaviors; (c) constraint of compensatory behaviors; and (d) a package of behavioral techniques designed to transfer therapeutic gains from the treatment to everyday setting. CI therapy has been shown in controlled studies to produce substantial improvement in function in motor disorders produced by several types of damage to the central nervous system and to produce widespread plastic changes in the organization and structure of the brain. Preliminary data suggest that CI therapy has an equivalent positive effect for motor deficit produced by TBI in military and civilian populations. This study is a rigorous, single blind, randomized controlled trial that compares the efficacy of CI therapy for improving use of the more-affected arm in adults with TBI to a holistic fitness program named Lakeshore Enriched Fitness Training (LEFT). Twenty-nine adults with TBI will be randomly assigned to each group. Participants in each group will receive 35 hours of training over two weeks, although the type of training, i.e., CI therapy vs. LEFT, will vary depending on group assignment. Assessment of more-affected arm motor function will be conducted at pre- and post-treatment and 1-year afterwards. On the same occasions, magnetic resonance imaging (MRI), diffusion tensor imaging (DTI), and functional MRI (fMRI) of the brain will be carried out to determine changes in white matter, grey matter, and functional brain activity. If neuroplastic changes parallel the expected changes in the more-affected arm, then the neuroimaging data will confirm the clinical data. In addition, the nature of the results from the neuroimaging studies may provide suggestions as to which types of neuroplasticity-inducing pharmacological agents, when combined with CI therapy, are most likely to yield a superior treatment outcome compared to CI therapy alone.

2. KEYWORDS

Constraint-Induced Movement therapy
neurorehabilitation
occupational therapy
physical therapy
traumatic brain injury
arm
hand
upper extremity
hemiparesis

neuroplasticity
magnetic resonance imaging
diffusion tensor imaging
fMRI

3. ACCOMPLISHMENTS

3a. What were the major goals of the project?

1. To compare the effect of CI therapy and LEFT training on motor function in TBI patients.
2. To determine whether the initial clinical treatment effect, if any, persists over time.
3. To ascertain whether plastic brain changes accompany whatever clinical changes that may result from CI therapy and LEFT, and whether the magnitude of the clinical and plastic brain changes are correlated.
4. To evaluate the effects of CI therapy and LEFT on return to work and quality of life on a preliminary basis.

Table 1. Milestones

Milestones	*Date Completed or Percent of Task Completed*
Year 1	
IRB approval for UAB and Lakeshore Foundation sites	Pre-award (3/26/14)
HRPO approval for these two sites	Pre-award (9/8/15)
IRB approval for VA recruitment sites	
Birmingham VAMC	Month 1 (10/22/14)
Richmond VAMC	Month 2 (11/11/14)
Denver VAMC	Month 4 (1/9/15)
HRPO approval for VA recruitment sites	
Birmingham VAMC	Month 6 (3/31/15)
Richmond VAMC	Month 6 (3/31/15)
Denver VAMC	Month 7 (4/2/15)
All personnel on board	Month 1
Data system set-up	Month 2
Enroll 11 participants	11 enrolled (100%)
Treat & pre- and post-test first 11 participants	9 completed (81%)
Year 2	
Enroll 33 additional participants	33 enrolled (100%)
Treat & pre- and post-test 33 participants	13 completed (39%)
Conduct 1-year follow-up testing for 11 participants	2 completed (18%)

Note. The milestones, i.e., completion targets, for tasks are from the most recent version of the statement of work, which is dated October 26, 2015 and has been approved by the DOD.

A small number of changes to the methods have been made since our application was submitted. All have already been described in our pre-award correspondence or quarterly progress reports and been reviewed with and approved by the Science Officer for this project or the HRPO or both. The changes, which are listed below, were all made in Year 1 except for the one described in the last bullet. All have been described in previous progress or annual reports.

- The original design for this RCT was a 2 x 2 factorial: Type of Therapy (CI therapy vs. LEFT) X Severity of Arm Motor Impairment (Mild-to-moderate vs. Moderate). A third factor was added after the award was made: Provision of Transfer Package (Standard vs. Enhanced). The Transfer Package is a set of behavioral techniques designed to facilitate transfer of gains from the treatment to everyday setting.
- Collection of data on the presence of variants of the gene that codes for BDNF was added. Animals with different variants of this gene have varying neuroplastic responses to training. We want to test whether the response to rehabilitation will vary among study participants with different variants of this gene.
- Housing of participants was split between the Lakeshore Foundation and our institution, the University of Alabama at Birmingham (UAB). All participants were originally to have been housed at the Lakeshore Foundation.
- The makeup of the VA recruitment sites was changed. Subcontracts were negotiated with the Birmingham VAMC, Denver VAMC, and Richmond VAMC.
- The option of collecting MRI data using a 1.5T scanner was added for participants for whom a 3T scanner is contraindicated but 1.5T is safe.
- The option of giving participants with anxiety about scanning a mild sedative agent was added.
- The collection of MRI scans was switched to a different set of scanners from the original instruments. This change was necessary because our University shut down the original scanners soon after the new scanners came on line. The new 3T scanner is a Siemens MAGNETOM Prisma 3T, which is considered state-of-the-art.

3b. What was accomplished under these goals?

The specific objectives in Year 1 were to obtain IRB and other regulatory approvals for the project, hire and train new personnel needed to round out the project team, refine and make final the study protocol, and recruit, enroll, treat, and test 11 participants. The specific objectives in Year 2 were to enroll, treat, and test an additional 33 participants and complete 1-year follow-up testing on the 11 participants planned for Year 1.

Major activities were in accord with these objectives. Table 1 shows that we obtained IRB and HRPO approval for study activities in Birmingham before the start of the award.

Although applications for approval of recruitment activities at our VA recruitment sites were submitted to their respective IRBs two-three months before the start of the award, IRB and HRPO approval was not obtained for the last VA recruitment site until Month 7 of the project. The study was registered with clinicaltrials.gov in Month 4. All study personnel were on board before the end of Month 1. Training and verification that personnel had appropriate knowledge of and skill in the study procedures was completed by end-Month 3. In addition, the protocol for the LEFT intervention was refined and an enhanced version of the set of behavioral techniques used in CI therapy for transferring therapeutic gains from the therapeutic setting to everyday life was developed. The key aspects of the database that warehouses the study data were completed by end-Month 2. In Months 4-6, three practice participants were treated and tested to ensure that coordination of the complex array of treatment and testing procedures was in order. In addition, in this quarter, step-by-step instructions were written up for all the study procedures and assembled in a manual of procedures (MOP; see Section 6c.1). In Months 7-9, a method was developed for generating synthetic neuroimaging data to permit evaluation of the sensitivity of the different types of structural MRI analyses proposed on the study (see Section 6c.2). In Months 6-12, 11 participants were enrolled. Treatment and pre-and post-testing were completed with 9 participants. One participant withdrew after being randomized to the LEFT intervention. The other was withdrawn by mutual consent of the project and the mother of the participant because the participant missed several treatment sessions.

In Year 2, 33 were enrolled. Treatment and pre- and post-testing were completed with 13 participants; 15 were scheduled for treatment and testing in Year 3. A total of 5 withdrew or were asked to withdraw. Three withdrew before pre-testing took place: one realized his work commitments did not permit participation in the project, one was a no show, and one had a spouse and psychiatrist who did not want him to take part in the study. One participant withdrew during pre-testing because he had to attend legal proceedings against him. Another was asked to withdraw during treatment because he missed or was very late for his treatment and testing sessions. One-year follow-up testing was completed with 2 of the 9 participants who completed treatment in Year 1. Follow-up testing is scheduled for 2 additional participants in Year 3, Quarter 1 and for 2 more participants in Year 3, Quarter 2. Two have not been able to commit to a date yet because of work or school commitments; however, the project is in contact with them and expect to be able to schedule a 1-year follow-up appointment shortly. One will not return phone calls from project personnel.

Recruitment of candidates for the study proceeded in parallel to these efforts. Since IRB and HRPO approval for recruitment of veterans with TBI at our VA sites was not yet granted, we initiated a major effort to recruit veterans in Alabama in Month 1 with the

assistance of Admiral Clyde Marsh, Commissioner, Alabama Department of Veterans Affairs. Admiral Marsh directed his team to distribute this project's recruitment materials to all 67 county offices in Alabama of AlaVetNet. In Month 2, UAB did a press release in connection with Veterans Day, which was followed by interviews with two local television stations about the project and opportunities for veterans to take part in it. In Month 3, a brief recruitment interview was taped with Admiral Marsh for airing on TV in Central Alabama on the program Veterans Affairs. We also placed color, 1/8 page ads in the Spring and Summer issues of US Veterans Magazine. In Year 2, the Brain Injury Association of American published a full page article in its newsletter describing the project, the inclusion and exclusion criteria, and the fact that the project would cover travel costs. Regrettably, these substantial efforts have yielded only a handful of contacts. It appears that outreach to the general community of veterans or civilians is too diffuse to reach our specific, target audience: veterans with TBI with motor impairment of one or both arms.

HRPO approval for recruitment activity at our three VA sites was received in Months 6 & 7. Recruitment efforts at these sites began shortly afterwards. The investigators at the three sites queried their electronic medical record system for the contact information of veterans with diagnostic and procedural codes reflecting a history of TBI and motor impairment of one or both arms. A cover letter, brochure, card to indicate interest, and stamped, addressed return envelope were mailed in batches of 100 to 500 to veterans who fit these criteria. Since HRPO approval was received for partner site recruitment activity, the Birmingham VAMC site mailed materials to 554 veterans. The Richmond VAMC site database search yielded 9,695 records, out of which 284 were determined to be likely enough candidates to mail a letter after review. The Denver VAMC site mailed materials to 13,451 veterans, out of which 172 were determined to be likely enough candidates to refer to UAB. In addition, in Month 6, the Director of the TBI Model Systems Center at UAB, Thomas Novack, PhD, who is an investigator on this project, mailed materials to approximately 100 civilians with TBI. (Dr. Novack has also directed patients under his care who appeared to be likely candidates to the study.) In Year 2, the TBI Model Systems Centers at Moss Rehabilitation Center in Philadelphia and Craig Hospital in Denver mailed materials to approximately 100 civilians each. This recruitment strategy, targeted mailings, has proven to be most productive.

The recruitment efforts above over the last two years have resulted in a total of 442 unique contacts of candidates with the project. Out of this number, telephone or videoconference screens were completed with 389 by end-Year 2; contact had not yet been made or preliminary screening was in still in process for 53. Out of 389, 236 did not pass the telephone or videoconference screen and 42 expressed lack of interest in taking part in the study. Out of the remaining 111 candidates, 44 have received

comprehensive, on-site screening, met study criteria, and agreed to take part in the study. The breakdown of reasons candidates did not qualify for the study after screening was: arm function too high (57%), did not have a TBI (20%), arm function too low (15%), health issues that prevented the candidate from participating in the study (6%), and problems with cognition, memory, or behavior severe enough to prevent participation in the study (2%).

The reasons that enrollment fell short of the targets in the original statement of work are discussed in Section 5b. The reasons treatment and testing is falling behind the targets for these activities is also discussed in this section.

Appendix A tables progress on data entry. For the pre- and post-treatment testing occasions, 100% of the clinical outcome data from participants who have completed treatment has been collected and entered, except for three measures. For the objective measure of amount of arm movement in daily life, i.e., accelerometry, data has not yet been collected at post-treatment from one participant. We are in the process of collecting these data now. For the general fitness test, data have been collected from all participants who have completed treatment. However, data entry has not been completed for 68% of these participants because of a changeover in personnel conducting this testing. The new tester has been trained in entry of the fitness testing data, and is now clearing up the backlog. For the Frontal Systems Behavioral Scale (FrSBe), pre- and post-treatment data are available from only 23% of the participants. The FrSBe is a measure of a participant's executive function that is completed by a family caregiver. We were not able to collect FrSBe data from the remaining participants because they did not travel to our University with a caregiver. Steps to remedy this problem are discussed in Section 5b. The FrSBe, however, is not one of the principal outcome measures for this project. MRI scans have only been collected from 27% of participants. As noted, follow-up data have only been collected from 2 of 9 participants who have reached their 1-year anniversary to date. Reasons for and steps to remedy the shortfall in MRI and 1-year clinical data collection are discussed in Section 5b.

Both the investigators and testing personnel on this project are blinded to exclude the possibility of experimenter bias from influencing the study results. Hence, none of the data collected have been analyzed to date with respect to the scientific questions reflected in the four main study goals. The data will be unblinded with respect to assignment to intervention group in the third year of the project. Analysis of the data with respect to the questions reflected in the study goals and write-up of these results in our progress and annual reports, along with dissemination of these results to the scientific, healthcare, and patient communities will take place then.

3c. What opportunities for training and professional development did the project provide?

This project does not have a formal training and professional development component. Training in the study procedures and in the conduct of research, however, has been provided to several staff members and students. Laura Reder, PTA, the blinded tester, has been trained to conduct the motor testing on a blinded basis. This training includes the Motor Activity Log and Wolf Motor Function Test, which are widely used in neurorehabilitation research, and the acquisition of data for kinematic studies of movement. Ms. Reder has also received training in the ethical conduct of research with humans. Brice Lambert, the data manager, has received training in processing the data from the movement monitors used to track changes in amount of movement of the more-affected arm in everyday life outside the laboratory and in searching the electronic medical records system in use at our University's health system and elsewhere. Michele Haddad, one of the graduate students who works on the analysis of the neuroimaging data, has received further mentoring in voxel-based morphometry, a method for quantifying changes in grey matter. Brent Womble, the other graduate student who works on the analysis of the neuroimaging data, has received mentoring in tract-based spatial statistics and Freesurfer, which are methods for quantifying changes in white matter and grey matter, respectively. Ms. Haddad and Mr. Womble have also received mentoring in experimental strategy, study design, and interpretation and writing up of data. Eight undergraduates, four on a work study basis and four on a volunteer basis, have received training in the ethical conduct of research with humans, the data entry and processing procedures, and in selected components of the study testing and treatment procedures.

3d. How were the results disseminated to communities of interest?

As noted, both the investigators and testing personnel on this project are blinded to exclude the possibility of experimenter bias from influencing the study results. Hence, analysis of the efficacy of the interventions tested and the write-up and dissemination of these results to the scientific, healthcare, and patient communities will have to wait until Year 3, when the study will be unblinded.

In the meantime, our recruitment efforts have increased awareness among veterans and the general public that impairment in the motor function of the arms after TBI may be amenable to treatment. Regrettably, little attention by healthcare professionals is paid to rehabilitation of motor function, particularly of the arms, after TBI because of the prominent nature of the cognitive impairments present after TBI. Hence, impairment of upper-extremity motor function often goes untreated and survivors live with persistent deficits. As noted, the project has been featured in several local television broadcasts, in a nationwide podcast, and in an article in the September, 2016 edition of the

newsletter of the Brain Injury Association of America. In addition, letters and recruitment brochures have been mailed to approximately 24,000 veterans and 5,000 brochures have distributed across the state of Alabama by AlaVetNet county offices. We believe these efforts are starting to change the view of patients with TBI, at least in Alabama, from nothing can be done to something needs to and can be done about upper-extremity motor impairment after TBI.

3e. What do you plan to do during the next reporting period to accomplish the goals?

In the next quarter, we plan to recruit, screen, enroll, test, and treat 6 participants. (See Section 5b for a discussion of this enrollment rate. Six rather than ten will be enrolled next quarter because of Thanksgiving in November and Christmas and other holidays in December.) Entry of the motor, quality of life, and other self-report data will continue, as will processing of the movement monitor data. Work on processing and analysis of the neuroimaging data, i.e., MRI, DTI, and fMRI scans, will also continue.

To ensure an adequate flow of participants, we plan to expand the recruitment efforts underway at the Denver VAMC. . Our partner recruitment site at the Denver VAMC has permission to mail information about the study to veterans outside of the Rocky Mountain VISN catchment area, and hence will double the number of letters it mails out to 600 per week. We request permission for the amount of the subcontract for the Denver VAMC be increased to $43,679 in Year 3 from $21,762 in Year 2 to support this activity. As noted, mailing letters to likely candidates for the study has been our most successful recruitment strategy, and in Year 2 has permitted us to hit our targets for enrollment. We will not renew the subcontract with our recruitment partner site atthe Richmond VAMC because that site has exhausted the pool of likely candidates for this project in their catchment area. We did the same with our recruitment partner at the Birmingham VAMC at the end of Year-1 for the same reason. Dr. Novack will continue to refer candidates to this project whom he encounters as Director of the TBI Model Systems Center at our University.

4. IMPACT

4a. What was the impact on the development of the principal discipline of the project?

Nothing to report. Please see explanation in the last paragraph of Section 3b**.**

4b. What was the impact on other disciplines?

Nothing to report. Please see explanation in the last paragraph of Section 3b**.**

4c. What was the impact on technology transfer?

Nothing to report. Please see explanation in the last paragraph of Section 3b**.**

4d. What was the impact on society beyond science and technology?
Please see the second paragraph of Section 3d**.**

5. CHANGES

5a. Changes in approach and reasons for change
Nothing to report. There have been no changes in our approach since the Year 2, Quarter 3 progress report.

5b. Actual or anticipated problems or delays and actions or plans to resolve them
We fell short of our Year 1 target for enrollment in our original statement of work because of a long delay in gaining approval to recruit through our 3 partner VA recruitment sites. The measures we undertook to address this shortfall were successful. We met our Year 2 target for enrollment, i.e., 33 individuals, in our revised statement of work dated October 26, 2015.

There was a long delay in gaining approval to recruit through our three VA recruitment sites in Year 1 because of multiple and lengthy administrative and regulatory hurdles to clear. Recruitment at the last VA site in Denver did not begin until May 18, 2015. These delays resulted despite our submitting the initial application for approval of this project to the IRB at UAB in January 2014, nine months before the start date of the award, and submitting initial versions of the applications for approval of recruitment activity at our three VA sites in June-July 2014, two-three months before the award start date. As reported previously, we initiated recruitment independently of our VA sites through the Department of Veterans Affairs in Alabama in October 2014 but that large effort, which involved distribution of recruitment brochures to all 67 AlaVetNeT county offices, among other measures, did not yield any candidates.

To address the shortfall in recruitment in Year 1, we expanded the recruitment activity that was originally planned for Year 2. At the Denver VAMC, the catchment area for candidates was expanded from the Denver VAMC to the entire VISN. At the Richmond VAMC, the original search of their electronic medical records limited the period to examined to 2005-2015; the search was expanded to 2001-2005. We sought the help of the TBI Model Systems Centers at Moss Rehabilitation Center in Philadelphia and Craig Hospital in Denver. Each center mailed materials to approximately 100 civilians each. We spoke about the project with Susan Conner, President of the Brain Injury Association of American. The Association published a full page article in its Fall newsletter about the project. As noted, the most successful form of outreach has been mailing a cover letter and brochure, along with a stamped, addressed return envelope,

to likely candidates. To meet our target for enrollment in Year 3, which is an 33 additional participants, we will, as noted, double the number of recruitment packets that are mailed out by the Denver VAMC to 600 per week. This recruitment source will not be exhausted since our recruitment partner site at the Denver VAMC has approval to mail letters to veterans outside of their VISN.

Although we met our enrollment target for Year 2, we fell short of the target for treating and testing participants. Thirteen were treated and completed pre- and post-treatment testing in Year 2 rather than 33. Only 13 were treated because the changes in the recruitment activities that we made bore fruit in the last half of the year. Many candidates were not able to schedule the 3-week stay in Birmingham needed to take part in the study close to the date they completed their telephone and videoconference screening. Hence, 15 participants were scheduled for treatment in Year 3. Five additional participants either withdrew or were asked to withdraw from the study. (See Section 3b for a discussion of the reasons for withdrawal.)

We expect to treat and complete pre- and post-treatment testing with 36 participants in Year 3. As noted, 15 are already scheduled for treatment in first and second quarter. And, we expect to recruit the same number of candidates in Year 3 that we did in Year 2, i.e., 33. We anticipate treating and testing 36 rather than 48 participants, i.e., 15 already scheduled plus 33 to be enrolled, because we assume that the proportion of withdrawals will be the same as experienced to date, i.e., 24%.

This plan will result in our reaching the enrollment target in the revised statement of work for the 3-year project period, i.e., 77. We anticipate completing treatment and pre- and post-treatment testing with a modestly smaller number of participants than planned, 58 vs. 62, because the withdrawal rate has been higher than anticipated, 24% vs. 20%. Nevertheless, there will be more than adequate power (> .99) to evaluate the first and most important specific aim of the study, which is to test whether CI therapy is an efficacious method for improving use in daily life of the more-affected of arm of adults with TBI. We also anticipate that there will be adequate power to evaluate the second specific aim, which is whether any gains observed at post-treatment persist. Although we have collected 1-year follow-up data from a smaller number of participants than planned to date (see Section 3b), we anticipate collecting long-term follow-up data on the Motor Activity Log (MAL), which is a measure of more-affected arm use in daily life, from at least 90% of the participants based on past experience with other CI therapy studies. We have been able to achieve this high long-term follow-up collection rate in past studies because the MAL can be administered over the telephone, permitting collection of this key outcome even if a participant cannot return to the laboratory for collection of the other measures. Since it is of advantage to collect data on all the

outcome measures, we first attempt to schedule a participant for return a visit within 3 months of their one-year anniversary. If we fail to do so, then we will schedule a MAL telephone interview even if it is outside the 3-month window. As described in our previous annual report and statement of work dated October 26, 2015, any 1-year follow-up data that remains to be gathered after end-Year 3 will be collected using carry-forward funds or funds available to our laboratory in our Department. The fourth aim of the study is evaluate the effect of CI therapy on return to work and quality of life on a preliminary basis. We have not experienced problems with the collection of the relevant measures, and expect to be able to evaluate these questions on a preliminary basis, as planned. We did not project adequate power to detect statistically significant differences between the study groups in the grant application because measures of economic productivity and quality of life are typically highly variable. Any trends observed will help to decide whether it would be worthwhile for future studies with larger sample sizes to examine the effects of CI therapy on these outcomes.

As noted, we have collected MRI scans from only 27% of the participants who have completed treatment (see Section 5b). The reason that scans were collected from only approximately a quarter of the participants is that many more participants than anticipated had shrapnel embedded in their bodies or medical implants, making it risky to a conduct a MRI scan. If this collection rate persists, a priori power calculations indicate that the number of scans available at the end of study may be inadequate to detect neuroplastic changes in the brain that may take place. However, we have detected and published statistically significant changes in brain structures after CI therapy in studies with only 9 and 10 participants per group. We detected widespread changes in grey matter and localized changes in white matter in the corticospinal tract and three other regions in 9 adults with multiple sclerosis who received CI therapy. We detected widespread changes in grey matter in 10 children with cerebral palsy who received pediatric CI therapy. Diffusion tensor imaging data was not collected with sufficient resolution in the children with cerebral palsy to permit detection of changes in white matter. At the current collection rate, we anticipate that there will 8 participants in each group in this project with valid pre- and post-treatment scans, which leaves open the possibility of detecting structural changes in the brain due to the study interventions.

Pre- and post-treatment scores are available from only 23% of the participants on the Frontal Systems Behavioral Scale (FrSBe), which as noted is a measure of executive function. We were only able to collect FrSBe data from this portion of participants because the FrBSe is administered to a family caregiver and many of our participants did not travel to our University with a caregiver. For future participants without a caregiver accompanying them to Birmingham, we will mail the FrSBe to their homes so that it can completed by a family caregiver, if the participant has one available and

agrees to permit the data to be collected in this way. The FrSBe, however, is not one of the principal outcome measures for this project. In addition, the Wisconsin Card Sorting Test, which is another test of executive function, has been administered to 100% of participants to date.

5c. Changes that had a significant impact on expenditures

We reported in our previous reports that funds were being expended at a slower rate than planned because of the delays that resulted in enrollment at a lower rate in Year 1 than projected. As of end-Year 2, expenditures registered for total costs were $1,162,833, with approximately $29,000 in charges still pending. The amount budgeted was $2,120,530. We plan to carry forward the unexpended funds, and use them to supplement the amount budgeted originally for Year 3, which was $544,230. This shift will allow enrollment, treatment, and testing to continue at the rate projected in Section 5b until end-Year 3. In addition, carryforward will remain at the end of Year 3. The carryforward will be used in a no-cost extension year to complete collection of one-year follow-up data; we anticipate that 36 participants will have their one year anniversary fall in the no-cost extension year. The carryforward will also be used to support writing up of the data and their submission for publication at a rapid pace.

5d. Significant changes in use or care of human subjects, vertebrate animals, biohazards, and/or select agents

Nothing to report. There have been no significant changes since the Year 2, Quarter 3 progress report. There have been no serious adverse events since the inception of the project. The risk-to-benefit ratio of the study has not changed. The Data & Safety Monitor for this project recommended a minor change in our telephone screening procedures at our meeting in Year 2, Quarter 4, which we will implement. We will now add a question to the screening interview that asks whether a legal guardian has been designated to make healthcare or other decisions for a candidate. If so, the telephone screen will not be conducted without the guardian present. The Data & Safety Monitor did not raise any other concerns that needed to be addressed.

6. PRODUCTS

6a. Publications, conference papers, and presentations

Nothing to report. As noted, both the testing personnel and investigators are blinded to assignment to intervention group until the last year of this project.

6b. Website or other Internet Site

We have developed a website for the purpose of recruiting participants. As noted, our recruitment activities have the benefit of increasing public awareness about the effects

of TBI on motor function of the upper-extremities and the possibility of remedying those impairments. The website address is: **www.tbirehabtherapy.net.**

6c. Technology or techniques

1. *A manual of procedures that describes the treatment and testing procedures in detail has been completed.* It was submitted along with our second quarter progress report. Work on a manuscript that introduces the protocol is underway. It will be submitted for publication to a high impact neurorehabilitation journal along with the manual of procedures in Year 3, Quarter 2. Dissemination of the manual of procedures will permit researchers to replicate our study and clinicians to implement the interventions tested, if found to be efficacious, in their practices.

2. *A method was developed for generating synthetic data to permit evaluation of the sensitivity of the different types of structural MRI analyses proposed on the study.* Longitudinal structural analyses attempt to detect use-dependent structural neuroplasticity at a gross anatomical level. Longitudinal voxel-based morphometry (VBM) is traditionally used to detect changes in volume or density of grey matter relative to other tissue. Surface-based morphometry (e.g. Freesurfer) reconstructs the edge of the grey matter and white matter into 3-dimensional surfaces, then measures geometric values, e.g. distance (thickness), surface area, volume, and curvature (gyrification). These two methods will be used on this project to study if and what types of neuroplastic change CI therapy and LEFT induce in veterans and civilians with TBI.

   Longitudinal VBM and surface-based morphometry may be differentially sensitive to different types of cellular and gross anatomical changes taking place in use-dependent structural reorganization of the brain. Hence, a method was developed by our laboratory in the last year for generating synthetic data to permit evaluation of the sensitivity of these two structural MRI analysis methods to the different types of structural changes that we anticipate in the brain as a result of the study interventions.

   We synthetically generated 3 longitudinal datasets with changes in each dataset isolated to a single gross anatomical (expansion or increased gyrification) or cellular (increased density) feature. All changes were made in the right superior frontal gyrus, using the anterior tip of the corpus callosum as a landmark. We used a point-based deformation technique to manually alter the shape of a gyrus. For cortical expansion, we pushed multiple points along the selected gyrus outward (**Fig. 1a**). For increased gyrification, we pushed two points along the selected gyrus inward, while keeping the overall shape of the gyrus intact (**Fig. 1b**). For increased density, we made a spherical region of the gyrus darker, with the change restricted to the grey matter (**Fig. 1c**). Finally, we processed these synthetic datasets using surface-based morphometry (Freesurfer 5.3), and we have begun to process the datasets using VBM (SPM12). Freesurfer accurately reconstructed the edge of the grey and white matter as the gyrus expanded and folded (**Fig. 1a-b**). Freesurfer did not detect the change in density (**Fig. 1c**). Preliminary VBM results suggest that SPM12 is more sensitive to changes in density than Freesurfer.

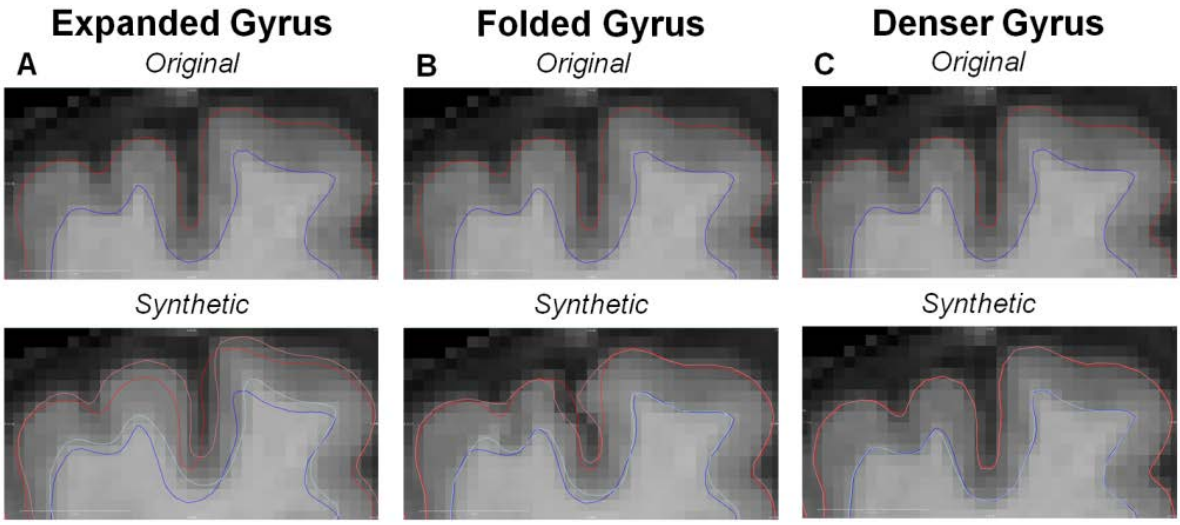

Figure 1. Freesurfer reconstruction of grey and white matter edges. The edges in the original brain are traced in red and blue. In the synthetic brains, the grey and white matter edges are traced in pink and light blue and are shown alongside the original traces.

This type of evaluation of imaging analysis methods has not been done to date. When this work is completed, a manuscript will be submitted to a high impact neuroimaging journal describing the method for generating synthetic data and its application to evaluating the sensitivity of voxel-based morphometry and measurement of cortical thickness using Freesurfer. We expect that the manuscript will be submitted in Year 3, Quarter 3.

6d. Inventions, patent applications, and/or licenses

Nothing to report.

6e. Other products

Nothing to report.

7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

7a. What individuals have worked on the project?

Name: Edward Taub, PhD
Project Role: Principal Investigator, UAB
Researcher Identifier: n/a
Nearest person month worked: 3
Contribution to project: He supervised the design, implementation, and conduct of all aspects of the project.

Name: Victor Mark, MD
Project Role: Medical Director, UAB
Researcher Identifier: ORCID ID 0000-0002-9468-7952
Nearest person month worked: 1
Contribution to project: He was responsible for the general medical supervision of participants in project procedures, carried out medical evaluations on all prospective participants, and supervised the administration of cognitive testing by project staff. He also participated in the design of the cognitive testing and the setup of the collection of neuroimaging data.

Name: Jerzy Szaflarski, MD, PhD
Project Role: Investigator/Neuroimaging Supervisor, UAB
Researcher Identifier: n/a
Nearest person month worked: 1
Contribution to project: Dr. Szaflarski designed the procedures for collection of structural magnetic resonance imaging (MRI) and resting state functional MRI.

Name: Jane Allendorfer, PhD
Project Role: Investigator, Neuroimaging Expert, UAB
Researcher Identifier: n/a
Nearest person month worked: 1
Contribution to project: Dr. Allendorfer designed the procedures for the collection of the diffusion tensor imaging (DTI) scans.

Name: David Morris, PhD
Project Role: Investigator, CIMT Training & Scoring Supervisor, UAB
Researcher Identifier: n/a
Nearest person month worked: 1
Contribution to project: Dr. Morris trained the Tester and ensured that she and others were able to perform the study procedures with adequate fidelity. He played in a major role in the design, implementation, and supervision of the LEFT intervention protocol. In addition, he wrote the manual of procedures in conjunction with the PI.

Name: James Rimmer, PhD
Project Role: Investigator, LEFT Intervention Supervisor, UAB
Researcher Identifier: n/a
Nearest person month worked: 1
Contribution to project: Dr. Rimmer designed the fitness testing procedures and assisted with the design of the LEFT intervention protocol.

Name: Gitendra Uswatte, PhD
Project Role: Investigator, Accelerometry & Data Analysis Supervisor, UAB
Researcher Identifier: ORCID ID 0000-0003-4507-7098
Nearest person month worked: 2
Contribution to project: He trained the Data Manager to collect and process the data from the movement monitors worn by participants and supervised the construction of the database for the study. He also took part in the design of the testing and treatment procedures, design and implementation of the recruitment procedures, and in the preparation of the regulatory documents for the study.

Name: Gary Cutter, PhD
Project Role: Investigator, Data Analysis Supervisor, UAB
Researcher Identifier: ORCID ID 0000-0002-8455-980X
Nearest person month worked: 1
Contribution to project: Dr. Cutter supervised the design of the randomization scheme and the construction of the database for the study.

Name: Thomas Novack, PhD
Project Role: Investigator, Recruiting & Cognitive Testing Supervisor, UAB
Researcher Identifier: n/a
Nearest person month worked: 1
Contribution to project: He assisted with the recruitment of patients and design of the cognitive and post-traumatic stress disorder testing procedures.

Name: Stephen Mennemeyer, PhD
Project Role: Investigator, Economic Analyst, UAB
Researcher Identifier: n/a
Nearest person month worked: 1
Contribution to project: He designed the procedures for collection economic and quality of life data.

Name: Staci McKay
Project Role: Trainer, UAB
Researcher Identifier: n/a
Nearest person month worked: 12
Contribution to project: She helped to design the enhanced Transfer Package procedures and has conducted recruitment and provided CI therapy in addition to coordinating work on the project on a day-to-day basis.

Name: Andrea Taylor
Project Role: Research Assistant, UAB
Researcher Identifier: n/a
Nearest person month worked: 12
Contribution to project: She helped to design the enhanced Transfer Package procedures and has conducted recruitment and provided CI therapy.

Name: Terrie Adams
Project Role: Trainer, UAB
Researcher Identifier: n/a
Nearest person month worked: 2
Contribution to project: She delivered the physical and mental fitness components of the LEFT intervention.
Source: Department of Psychology, UAB

Name: Jennifer Zimmerman
Project Role: Research Assistant, UAB
Researcher Identifier: n/a
Nearest person month worked: 1
Contribution to project: She delivered the massage therapy component of the LEFT intervention for a portion of the participants.

Name: Robin Shafer
Project Role: Research Assistant, UAB
Researcher Identifier: n/a
Nearest person month worked: 3
Contribution to project: She delivered the massage therapy component of the LEFT intervention for the remaining participants.

Name: Laura Reder
Project Role: Research Assistant, UAB
Researcher Identifier: n/a
Nearest person month worked: 8
Contribution to project: She conducted the blinded motor and other clinical testing of the participants and conducted on-site screening of participants in conjunction with the Medical Director.

Name: Michelle Haddad
Project Role: Graduate Student, UAB
Researcher Identifier: n/a
Nearest person month worked: 5
Contribution to project: She assisted with collection of the neuroimaging data and development of a method for evaluating the sensitivity of the neuroimaging methods proposed for assessing changes in grey matter.

Name: Brent Womble
Project Role: Graduate Student, UAB
Researcher Identifier: n/a
Nearest person month worked: 6
Contribution to project: He assisted with collection and processing of the neuroimaging data and developed a method for evaluating the sensitivity of the neuroimaging methods proposed for assessing changes in grey matter.
Source: Department of Psychology, UAB

Name: Brice Lambert
Project Role: Data Manager, UAB
Researcher Identifier: ORCID ID 0000-0003-1947-1569
Nearest person month worked: 7
Contribution to project: He constructed the database that holds the data from this project, set-up the movement monitors to collect data and processed the data collected, and conducted random assignment of participants to the study groups.

Name: Ryan Lee
Project Role: Research Assistant (regulatory documents, recruitment), UAB
Researcher Identifier: n/a
Nearest person month worked: 3
Contribution to project: He helped to prepare and maintained the regulatory documents, ordered equipment and supplies, and assisted with recruitment, including design of the website and recruitment materials for the study.

Name: Cassie Self (effective 02/2016)
Project Role: Research Assistant (regulatory documents, recruitment), UAB
Researcher Identifier: n/a
Nearest person month worked: 7
Contribution to project: Ms. Self replaced Mr. Lee. She performed the same activities.

Name: Jeff Underwood
Project Role: Subcontract Principal Investigator, Lakeshore Foundation
Researcher Identifier: n/a
Nearest person month worked: 1
Contribution to project: Oversight of activities at the Lakeshore Foundation. The LEFT intervention was conducted on the campus of the Lakeshore Foundation. In addition, participants in the LEFT group were housed there.

Name: Laurie Berenotto
Project Role: Cottage Coordinator, Lakeshore Foundation
Researcher Identifier: n/a
Nearest person month worked: 2
Contribution to project: She facilitated the stay of the study participants on the campus of the Lakeshore Foundation.

Name: Lisa Brenner, PhD
Project Role: Subcontract Principal Investigator, Denver Research Institute
Researcher Identifier: ORCID ID 0000-0002-2629-214X
Nearest person month worked: 1
Contribution to project: Oversight of all activities at the Denver VAMC recruitment site.

Name: Kelly Stearns
Project Role: Recruitment Coordinator, Denver Research Institute
Researcher Identifier: ORCID ID 0000-0002-2629-214X
Nearest person month worked: 1
Contribution to project: She assembled the mailing list, mailed out letters to study candidates, answered telephone calls from candidates with questions about the mailing, and assisted with preparation of the regulatory documents for this site.

Name: Treven Pickett, PsyD
Project Role: Subcontract Principal Investigator, McGuire Research Institute
Researcher Identifier: n/a
Nearest person month worked: 1
Contribution to project: Oversight of all activities at the Richmond VAMC recruitment site.
Source: Richmond VAMC

Name: David Rothman
Project Role: Recruitment Coordinator, McGuire Research Institute
Researcher Identifier: n/a
Nearest person month worked: 3
Contribution to project: He reviewed the medical records, assembled the mailing list, mailed out letters to study candidates, answered telephone calls from candidates with questions about the mailing, and assisted with preparation of the regulatory documents for this site.

7b. Has there been a change in the active other support of the PI or senior/key personnel since the last report period?

Victor Mark, Investigator
Interactive Immersive Virtual Reality Walking for SCI Neuropathic Pain (Trost)
0.24 calendar months
Kim Cerise, Director of Grants Management
Craig Nielsen Foundation
16830 Ventura Blvd
Encino, CA 91436
Performance Period: 8/31/2016-8/30/2018
Annual Direct Costs: $149,999
This project designs and test an immersive virtual reality treatment method to control neuropathic pain following traumatic spinal cord injury.
This is a new project. There is no overlap. Participation in the project that is the subject of this report will not be impeded by this activity.

Jerzy Szaflarski, Investigator
Quality of Epilepsy Treatment and Costs in Older Americans by Race (QUIET CARE)
(Pisu, PI)
0.0 calendar months
National Institutes of Health/NINDs
P.O. Box 5801
Bethesda, MD 20824
Award# R01 NS080898
Performance Period: 10/01/2012-08/31//2016
Annual Direct Cost: $11,555
Role: Co-Investigator
The goal for this study is to investigate quality of epilepsy care provided to older patients with particular attention to geographic and racial disparities.

Aim1: Assessing quality of AED treatment for different racial groups of Medicare beneficiaries with epilepsy; Aim 2: Determining the quality of care after seizure recurrence for different racial groups of Medicare beneficiaries with epilepsy; Aim 3: Determining if lower health care cost are associated with QUIET concordant care across racial groups are very important and address issues plaguing epilepsy patients for a long time.
This award has ended since the last annual report. Dr. Szaflarski will no longer be committing effort to this project.

Post-stroke aphasia and rTMS treatment (PART) (Szaflarski, PI)
3.0 calendar months
National Institutes of Health
Grants Officer: Mary E. Michel
BT 6100 Rm. 8A17C
6100 Executive Blvd
Rockville, MD 20852
Award# R01HD068488
Performance Period: 01/01/2012-12/30/2016
Annual Direct Cost: $378,384
The goal of this study is to conduct randomized, blinded, sham controlled trial of excitatory rTMS for the treatment of post-stroke aphasia
Aim 1: To determine the comparative efficacy and optimal dosing of nerTMS on aphasia recovery using a randomized, double-blind, sham-controlled study design; Aim 2: To use fMRI to assess changes in language lateralization in response toner TMS; Aim 3: To explore the possible synergistic effect of constraint induced aphasia therapy (CIAT) plus nerTMS on aphasia recovery in a group of 20 LMCA stroke patients.
Dr. Szaflarski will no longer be committing effort to this project.

Imaging the effect of centrotemporal spikes and seizures on language in children (Vannest, PI)
0.0 calendar months
Children's Hospital Medical Center Cincinnati/NIH
3333 Burnet Avenue, ML 7030
Cincinnati, Ohio 45229-3030
Award# R01 NS065840
Performance Period: 08/01/2011-07/31/2016
Annual Direct Costs: $4,654
Role: Subcontract PI
The goal of this study is to evaluate the cognitive and neural effects of centrotemporal spikes on language performance and the efficacy of medical treatment with

carbamazepine or levetiracetam on long-term linguistic abilities in patients with benign epilepsy with centrotemporal spikes (BECTS).
This award has ended since the last annual report. Dr. Szaflarski will no longer be committing effort to this project.

Presurgical applications of fMRI in epilepsy (Binder, PI)
0.12 calendar months
Medical College of Wisconsin/NIH
8701 Watertown Plank Road
Milwaukee, WI 53226-3548
Award# R01 NS035929
Period of Performance: 07/01/2011-06/30/2017
Annual Direct Cost: $13,034
Role: Subcontract PI
Abstract: The goal of this study is to assess the predictive value of fMRI for post-surgical language outcomes.
This award is in a no cost extension, effort for Dr. Szaflarski has been decreased. There is no overlap. Participation in the project that is the subject of this report will not be impeded by this activity.

Human Epilepsy Project (HEP) (Bebin, PI)
0.0 calendar months
Epilepsy Study Consortium
2325 Dulles Corner Boulevard, Suite 670
Herndon, VA 20171
Period of Performance: 08/06/2013-08/05/2018
Annual Direct Cost: $8,000
Role: Subcontract Co-PI
The goal is to identify clinical characteristics and biomarkers predictive of disease outcome, progression, and treatment response in participants with new onset or recently diagnosed focal epilepsy.
Dr. Szaflarski will no longer be committing effort to this project, enrollment has ended.

RNS System Post-Approval Study in Epilepsy (Szaflarski, PI)
0.12 calendar months
NeuroPace, Inc.
455 N. Bernardo Avenue
Mountain View, CA 94043
Period of Performance: 05/08/2015-05/07/2022
Direct Costs: $197,127

The primary objective is to follow patients prospectively over 5 years in the real-world environment to gather data on the long-term safety and effectiveness of the RNS System at qualified Comprehensive Epilepsy Centers by qualified neurologists, epileptologists, and neurosurgeons trained on the RNS System.
Dr. Szaflarski's effort has decreased on this award. There is no overlap. Participation in the project that is the subject of this report will not be impeded by this activity.

An Open-label Study to Evaluate the Safety, Efficacy, and Pharmacokinetics of SAGE-547 Injection as Adjunctive Therapy for the Treatment of Super-Refractory Status Epilepticus (Szaflarski, PI)
0.48 calendar months
Sage Therapeutics
215 First Street
Cambridge, MA 02412
Period of Performance: 05/20/2014-05/29/2018

Direct Costs: $ 66,941
The primary objective is to evaluate the safety and tolerability of SAGE-547 Injection (SAGE-547) in subjects in super-refractory status epilepticus (SRSE)
Dr. Szaflarski's effort has increased on this award. There is no overlap. Participation in the project that is the subject of this report will not be impeded by this activity.

Perampanel as a neuroprotective and antiepileptic compound in animal model of TBI (Szaflarski, PI)
0.24 calendar months
Eisai Inc.
100 Tice Boulevard
Woodcliff Lake, NJ 07677
Period of Performance: 07/01/2016-06/30/2017
Direct Cost: $172,917
The first primary objective of the study is to evaluate the effect of PRM on acute and sub-acute biomarkers and indices of neuroprotection in a rodent model of TBI (fluid percussion model). The secondary primary objective is to evaluate the effects of PRM on reduction of TBI-induced acute seizures in the same rodent model of TBI.
This award is new. There is no overlap. Participation in the project that is the subject of this report will not be impeded by this activity.

Understanding hippocampal internal architecture in human temporal lobe epilepsy -- from MRI to epigenetics (Ver Hoef, PI)
0.6 calendar months
Stephanie Mitchell
National Institutes of Health, NINDS
6001 Executive Boulevard, Room 8184, MSC 9537
Bethesda, MD 20892-9537
Period of Performance: 07/01/2016-06/30/2021
Annual Direct Cost: $417,378
Role: Co-Investigator
The goal of this project is to better detect, characterize, and understand the pathologic changes of the epileptic hippocampus through correlation of advanced imaging data with clinical and basic scientific data.
This award is new. There is no overlap. Participation in the project that is the subject of this report will not be impeded by this activity.

Probing and Understanding the Brain: Micro and Macro Dynamics of Seizure and Memory Network (Iasemidis, PI)
0.6 calendar months
Louisiana Tech University/NSF
P.O. Box 3092, Ruston, LA 71272
Contract# 32-0965-54132-UAB
Period of Performance: 09/01/2016-08/31-2020
Annual Direct Cost: $359,382
Role: Site PI
The goal is to bridge the electrophysiological and neurochemical domains with high fidelity, resolution, sensitivity, and specificity; to develop a deep understanding of the role of neuro biomarker signaling in underlying dynamics of brain transitions at micro and macro levels and thus gain new fundamental insights into brain function.
This award is new. There is no overlap. Participation in the project that is the subject of this report will not be impeded by this activity.

Stephen T. Mennemeyer, Investigator
Improving Access to and Quality Eye Care in an At-Risk, Underserved Population
.24 calendar
Centers for Disease Control and Prevention
1U58DP002651-03 (Owsley)
Performance Period: 09/30/12-09/29/15
Annual Direct Costs: $250,000
The focus of our translational research center is on a high-risk yet underserved segment

of the ≥ 40 years old population, namely African Americans residing in Jefferson County, Alabama, many of whom are uninsured. Our research projects will assess system-level and individual level factors that impact access to and quality of eye care, and will identify barriers and enablers to efficacious and cost-effective eye care.
Role: Co-Investigator
Contracting Officer: JOHN E. CREWS, D.P.A.
Centers for Disease Control and Prevention
1600 Clifton Road, E-88
Atlanta, GA 30333
Phone: 404-498-3013, Fax: 404-498-3060, E-mail WZC0@cdc.gov.
This project has ended, Dr. Mennemeyer is no longer committing time to this project.

Research and Analysis for Alabama Medicaid
.60 calendar
Alabama Medicaid Agency 09-058 (Morrisey), #08-058 (Bronstein), C7062155 (Blackburn) Performance Period: 07/01/10-06/30/17
Annual Direct Costs: 2013-2016-$60,000; 2016-2017- $90,000
Develop staff expertise in accessing and using AL Medicaid claims data. Second, it will provide analysis of AL Medicaid data to address programmatic and policy questions raised by this state agency.
Role: Co-Investigator
Contract Officer: Amanda Mitchell
Alabama Medicaid Agency
PO Box 5624 Montgomery, Alabama 36103-5624
phone: (334) 242-5000, email: Amanda.mitchell@medicaid.alabama.gov
Ongoing project, renewed each year. There is no overlap. Participation in the project that is the subject of this report will not be impeded by this activity.

Anniston Community Health Survey (ACHS): Follow-up Study and Dioxin Analysis
3.0 calendar
Centers for Disease Control and Prevention
200-2011-40834 (Mennemeyer)
Performance Period: 05/01/11-09/30/14
Annual Direct Costs: $252,605
Residents of Anniston Alabama who were exposed to high levels of industrial polychlorinated biphenyls (PCBs) from 1929-1977 have been followed by the CDC to determine the effects on their health of this exposure. The current study is will re-survey approximately 600 individuals from whom serum samples were obtained from 2005-2007. UAB's Survey Research Unit (SRU) provided the framework and staff for the original survey and will now conduct a follow up survey with further collection of serum samples.

This project has ended, Dr. Mennemeyer is no longer committing time to this project.

Evaluation of the Alabama Health Information Exchange (AHIE) Cooperative Agreement Program
3.60 calendar
Alabama Medicaid Agency
12-178 (Mennemeyer)
Performance Period: 07/01/12-12/31/13
Annual Direct Costs: $363,573
To determine how well the Alabama Health Information Exchange is working at connecting providers and consumers in an electronic network to share health care information and improve health outcomes.
This project has ended, Dr. Mennemeyer is no longer committing time to this project.

Proficient Glaucoma Care Delivery Model Based on Automated Structural and Function
1.2 calendar
Centers for Disease Control and Prevention
U58DP004061-01 (Girkin)
Performance Period: 09/30/12 – 09/29/15
Annual Direct Costs: $646,460
The purpose of this project is to develop and implement a community-based cost-efficient glaucoma detection and longitudinal care delivery model for glaucoma targeting the at-risk African American population ≥ 40 years old.
Role: Co-Investigator
Contracting Officer: John E. Crews, D.P.A.
Centers for Disease Control and Prevention
1600 Clifton Road, E-88, Atlanta, GA 30333
Phone: 404-498-3013, Fax: 404-498-3060, E-mail WZC0@cdc.gov.
This project has ended, Dr. Mennemeyer is no longer committing time to this project.

A Simulation Model for Understanding Prevention and Treatment of Depression Among HIV+ Women
1.80 Calendar
National Science Foundation/AHRQ
CMMI-1233652 (Mennemeyer)
Performance Period: 09/01/12-08/31/16
Annual Direct Costs: $321,960
This project examines the allocation of resources to the treatment and prevention of HIV/AIDS and the role of screening and treatment for depression among women living with HIV (WLWH).

Role: PI
Contracting Officer: Diwakar Gupta
CMMI Div Of Civil, Mechanical, & Manufact Inn ENG Directorate for Engineering
The National Science Foundation
4201 Wilson Boulevard
Arlington Virginia 22230
phone: (703) 292-8360 email: dgupta@nsf.gov
This project has ended, Dr. Mennemeyer is no longer committing time to this project.

5P30-AI027767 Saag (PI) 6/01/14-05/31/19 .60 CM
NIH/NIAID $1,279,523
UAB Center for AIDS Research
The primary purpose of this center is to support interdisciplinary AIDS research efforts. This Center is responsible for the planning, evaluating, managing and documenting a broad array of research activities within the two institutions.
The purpose of this project is linking clinical and basic science studies through the use of shared facilities and to translate as quickly as possible fundamental knowledge about AIDS and its related disorders into clinical treatment and prevention programs.
Biostatistics and Analysis Core D- Specific Aims:
1. Encompass the traditional role for a Biostatistics and Analysis Core along with our expanding roles in the enhanced focus on clinical outcomes research and community outcomes research. Leveraging of resources and synergy with other CFAR Cores will contribute to substantial growth in HIV infection research.
Role: Co-Investigator
Contracting Officer: Mrs. Deanna L Ingersoll
NIAID (National Institute of Allergy and Infectious Diseases)
BG 5601FL RM 4G61 5601 FISHERS LN
ROCKVILLE MD 20852 Mailstop 9833,
phone: 240-669-2989 FAX: 301-493-0597 email: deanna.ingersoll@nih.gov
This is a new project. There is no overlap. Participation in the project that is the subject of this report will not be impeded by this activity.

C1600000006 Rucks (PI) 11/15/15-11/14/16 0.30 CM
Alabama Medicaid Agency $638,167
Alabama Medicaid CAHPS Health Plan Survey
The purpose is to collect CAHPS (Consumer Assessment of Health Providers and Systems) Health Plan Survey data to assess the experiences of care among Medicaid beneficiaries in Alabama. Objectives: Medicaid is interested in administering the CAHPS Health Plan Survey to assess beneficiaries' experiences with care.
Role: Co-Investigator
Contracting Officer: Chris McInnish
Alabama Medicaid Agency
Managed Care Division
PO Box 5624 Montgomery, Alabama 36103-5624

Phone 334-353-3216, email Chris.McInnish@medicaid.alabama.gov
This is a new project. There is no overlap. Participation in the project that is the subject of this report will not be impeded by this activity.

Lisa Brenner, Investigator
Longitudinal assessment of the influence of lifestyle homogenization on the MoBE in a cohort of United States Air Force Cadets (Lowry PI)
0.60 calendar months
Alfred P. Sloan Foundation
Paula Olsiewski
630 Fifth Avenue, Suite 2550
New York, NY 10111
07/01/16-12/31/17
$509,015
The goal of the project is to quantify dynamic feedback between human and built environment microbiomes, through longitudinal characterization of cohabitation in human populations.
Aim 1. Quantify the impact of lifestyle homogenization on the dynamic microbial exchange between people and the BE.
This is a new project. There is no overlap. Participation in the project that is the subject of this report will not be impeded by this activity.

Biological Signature and Safety of an Immunomodulatory Probiotic Intervention for Veterans with Co-Occurring Mild TBI and PTSD (Brenner PI)
Rehabilitation Research and Development Service
Stuart Hoffman, PhD
Department of Veterans Affairs
810 Vermont Avenue, NW (10P9R)
Washington, DC 20420
06/01/16-05/30/18
$199,960
The goal of the proposed project is to investigate the effects of an immunoregulatory probiotic on biological signatures of systemic inflammatory processes (plasma concentrations of proinflammatory cytokines/chemokines), as well as proximal signatures of probiotic administration including microbial diversity and community level shifts in the gut microbial composition, and changes in gut permeability in Operation Enduring Freedom/Operation Iraqi Freedom/Operation New Dawn (OEF/OIF/OND) Veterans with co-occurring PPC and PTSD symptoms, and elevated baseline inflammation (plasma C-reactive protein [CRP] > 3.0 mg/L).
Aim 1. Determine the effects of L. reuteri on biological signatures of gut microbiota, gut permeability, systemic inflammation processes, and stress responses.

Aim 2. Determine the feasibility of L. reuteri supplementation.
Aim 3. Determine the acceptability of L. reuteri supplementation.
Aim 4. Determine the tolerability and safety of L. reuteri supplementation.
This is a new project. There is no overlap. Participation in the project that is the subject of this report will not be impeded by this activity.

Military Suicide Research Consortium 2.0 (Gutierrez & Joiner PI)
0.3 calendar months
DoD, Military Operational Medicine Research
Michelle Lane
Military Operational Medicine Research Program
504 Scott Street
Fort Detrick, MD 21702
03/01/16-02/28/21
$9,939,843
The major goal of this project is to synchronize and integrate suicide prevention efforts.
Aim 1. Produce new scientific knowledge about suicidal behavior in the military.
Aim 2. Use high-quality research methods/analysis to positively impact policy and practice.
Aim 3. Disseminate Consortium information and findings to those accountable for ensuring mental health of military personnel.
This is a new project. There is no overlap. Participation in the project that is the subject of this report will not be impeded by this activity.

Toxoplasma gondii, the kynurenine pathway, and suicidal behavior in veterans (Postolache, PI)
0.60 calendar months
Clinical Science Research and Development
Veterans Health Administration Office of Research and Development
Theresa Gleason, Ph.D.
810 Vermont Avenue, NW
Washington, DC 20420
07/01/16-06/30/21
$625,769
The main goal of this project is to compare T. gondii seropositivity, KYN and its metabolites QUIN and PIC, and inflammation markers in Veterans who receive mental health services vs. those without a history of suicidal self-directed violence.
Aim 1. To demonstrate a link between *T. gondii* IgG seropositivity and high-lethality SSDV in Veterans.
Aim 2. To establish a link between kynurenines and high-lethality SSDV in Veterans.

Aim 3. To investigate associations of *T. gondii* seropositivity with trait aggression composite score and performance on neuropsychological tests including decision making, measures of executive functioning, previously have been associated with SSDV.
This is a new project. There is no overlap. Participation in the project that is the subject of this report will not be impeded by this activity.

7c. What other organizations were involved as partners?
Organization Name: Alabama Department of Veterans Affairs
Location of Organization: 1815 Cogswell Ave #132, Pell City, AL 35125
Partner's contribution to the project: Collaboration. This partner posted recruitment materials in all of their county offices.

Organization Name: UAB TBI Model Systems
Location of Organization: 529 Spain Rehabilitation Center,1717 6th Avenue South Birmingham, AL 35249-7330
Partner's contribution to the project: Collaboration. This partner mailed recruitment materials to candidates for this study to adults with TBI in their patient registry.

Organization Name: The Moss Traumatic Brain Injury Model System
Location of Organization: 5o Township Line Rd, Elkins Park, PA 19027
Partner's contribution to the project: Collaboration. This partner mailed recruitment materials to candidates for this study to adults with TBI in their patient registry.

Organization Name: The Rocky Mountain Regional Brain Injury System
Location of Organization: 3425 S Clarkson St, Englewood, CO 80113
Partner's contribution to the project: Collaboration. This partner mailed recruitment materials to candidates for this study to adults with TBI in their patient registry.

Organization Name: Brain Injury Association of America
Location of Organization: 1608 Springhill Rd, Ste 110, Vienna, VA 22182
Partner's contribution to the project: Other. This BIAA featured an article about the project in its Fall 2016 newsletter.

Organization Name: Alabama AHEC
Location of Organization: 930 20th Street South, Room 307, Birmingham, AL 35205
Partner's contribution to the project: Facilities. This partner permitted project staff to host a booth promoting our study at a community fair for veterans and the organizations that provide services to veterans in Birmingham, AL.

Organization Name: Greater Birmingham Republican Women
Location of Organization: P.O. Box 43922, Birmingham, AL 35243
Partner's contribution to the project: Other. This partner hosted a presentation about the project by the PI and Co-investigator Uswatte at their monthly meeting with the aim of galvanizing community resources to support the project.

8. SPECIAL REPORTING REQUIREMENTS

None.

9. APPENDICES

Appendix A. Tables on Progress of Data Collection

Appendix A

Tables on Progress of Data Collection

Table 1. Key to Data Collection Tables

Table 2. Clinical Data Collection

Table 3. Brain Scan Collection

Key to Data Collection Tables

Abbreviation in Table	Full Name or Explanation	Parameter Assessed
MAL	Motor Activity Log	real world more-affected arm use
WMFT	Wolf Motor Function Test	more-affected upper extremity motor ability
accel	wrist-worn accelerometry	real world more-affected arm movement
ashworth	Modified Ashworth Scale	more-affected arm spatisticity
FrSBe	Frontal Systems Behavior Scale	family member/caregiver rates behavior of patient to assess quality and quantity of problems caused by frontal lobe damage
HUI-3	Multi-Attribute Health Status Classification System: Health Utilities Index Mark 3	quality of life
MMSE	Mini-Mental Status Exam	cognitive impairment
PCL-5	PTSD Checklist for DSM-5	PTSD
ROM	Range of Motion	active range of motion of more-affected arm
SWLS	Satisfaction With Life Scale	assessment of life satisfaction
TBI model systems	TBI Model Systems Intake Interview	quality of life
WCST	Wisconsin Card Sorting Task	executive function
WMS digit span	Wechsler Memory Scale Digit Span	working memory
WMS logical memory	WMS recall of details of a short narrative	narrative memory
WMS visual reproductior	WMS Visual Memory scale	visual memory
Fitness assessment	Fitness assessment	full body fitness assessment
pre	Pre-treatment	
post	Post-treatment	
f/u 1 yr	1-year follow-up	
YY	data collected and entered	
Y	data collected but not entered	
.	data missing, i.e., data not collected	
n/a	test date has not yet occurred	

Participant	status	MAL pre	MAL post	MAL f/u 1 yr	WMFT pre	WMFT post	WMFT f/u 1 yr	accel pre	accel post	accel f/u 1 yr
5201	follow up complete	YY	YY	YY	YY	YY	YY	YY	YY	YY
5202	treatment complete	YY	YY	n/a	YY	YY	n/a	YY	YY	n/a
5203	treatment complete	YY	YY	n/a	YY	YY	n/a	YY	YY	n/a
5204	treatment complete	YY	YY	n/a	YY	YY	n/a	YY	YY	n/a
5205	treatment complete	YY	YY	n/a	YY	YY	n/a	YY	YY	n/a
5206	treatment complete	YY	YY	n/a	YY	YY	n/a	YY	YY	n/a
5207	treatment complete	YY	YY	n/a	YY	YY	n/a	YY	YY	n/a
5208	treatment complete	YY	YY	n/a	YY	YY	n/a	YY	YY	n/a
5211	treatment complete	YY	YY	n/a	YY	YY	n/a	YY	YY	n/a
5212	follow up complete	YY	YY	YY	YY	YY	YY	YY	YY	YY
5213	treatment complete	YY	YY	n/a	YY	YY	n/a	YY	YY	n/a
5214	treatment complete	YY	YY	n/a	YY	YY	n/a	YY	YY	n/a
5215	treatment complete	YY	YY	n/a	YY	YY	n/a	YY	YY	n/a
5217	treatment complete	YY	YY	n/a	YY	YY	n/a	YY	YY	n/a
5218	treatment complete	YY	YY	n/a	YY	YY	n/a	YY	YY	n/a
5219	treatment complete	YY	YY	n/a	YY	YY	n/a	YY	YY	n/a
5222	treatment complete	YY	YY	n/a	YY	YY	n/a	YY	YY	n/a
5227	treatment complete	YY	YY	n/a	YY	YY	n/a	YY	YY	n/a
5228	Treatment complete	YY	YY	n/a	YY	YY	n/a	YY	YY	n/a
5232	treatment complete	YY	YY	n/a	YY	YY	n/a	YY	YY	n/a
5233	Treatment complete	YY	YY	n/a	YY	YY	n/a	YY	.	n/a
5237	treatment complete	YY	YY	n/a	YY	YY	n/a	YY	YY	n/a
% Completed		100	100	9	100	100	9	100	95	9

Note. Our data quality assurance protocol dictates that the person who filled out the physical form should be the one to enter the data. Data in database is compared it to physical form by personnel from study other than the person who entered it.

Key to Codes in Table Cells. YY = data collected and entered; Y = data collected but not entered; . = data missing, i.e., data not collected; n/a = test date has not yet occurred.

Participant	status	Ashworth pre	Ashworth post	Ashworth f/u 1 yr	FrSBe Pre	FrSBe Post	HUI - 3 pre	HUI_3 Post	HUI-3 F/u 1 ur	MMSE pre	PCL-5 pre	PCL-5 Post
5201	follow up complete	YY	YY	YY	.	.	YY	YY	YY	YY	YY	YY
5202	treatment complete	YY	YY	n/a	.	.	YY	YY	n/a	YY	YY	YY
5203	treatment complete	YY	YY	n/a	YY	YY	YY	YY	n/a	YY	YY	YY
5204	treatment complete	YY	YY	n/a	.	.	YY	YY	n/a	YY	YY	YY
5205	treatment complete	YY	YY	n/a	.	.	YY	YY	n/a	YY	YY	YY
5206	treatment complete	YY	YY	n/a	YY	YY	YY	YY	n/a	YY	YY	YY
5207	treatment complete	YY	YY	n/a	YY	.	YY	YY	n/a	YY	YY	YY
5208	treatment complete	YY	YY	n/a	.	.	YY	YY	n/a	YY	YY	YY
5211	treatment complete	YY	YY	n/a	YY	YY	YY	YY	n/a	YY	YY	YY
5212	follow up complete	YY	YY	YY	.	.	YY	YY	YY	YY	YY	YY
5213	treatment complete	YY	YY	n/a	.	.	YY	YY	n/a	YY	YY	YY
5214	treatment complete	YY	YY	n/a	.	.	YY	YY	n/a	YY	YY	YY
5215	treatment complete	YY	YY	n/a	.	.	YY	YY	n/a	YY	YY	YY
5217	treatment complete	YY	YY	n/a	.	.	YY	YY	n/a	YY	YY	YY
5218	treatment complete	YY	YY	n/a	.	.	YY	YY	n/a	YY	YY	YY
5219	treatment complete	YY	YY	n/a	YY	.	YY	YY	n/a	YY	YY	YY
5222	treatment complete	YY	YY	n/a	.	.	YY	YY	n/a	YY	YY	YY
5227	treatment complete	YY	YY	n/a	.	.	YY	YY	n/a	YY	YY	YY
5228	Treatment complete	YY	YY	n/a	.	.	YY	YY	n/a	YY	YY	YY
5232	treatment complete	YY	YY	n/a	.	.	YY	YY	n/a	.	YY	YY
5233	Treatment complete	YY	YY	n/a	YY	YY	YY	YY	n/a	YY	YY	YY
5237	treatment complete	YY	YY	n/a	.	.	YY	YY	n/a	YY	YY	YY
% Completed		100	100	9	27	23	100	100	9	86	100	100

Note. Our data quality assurance protocol dictates that the person who filled out the physical form should be the one to enter the data. Data in database is compared it to physical form by personnel from study other than the person who entered it.

Key to Codes in Table Cells. YY = data collected and entered; Y = data collected but not entered; . = data missing, i.e., data not collected; n/a = test date has not yet occurred.

Participant	status	PCL-5 f/u 1 yr	ROM pre	ROM Post	ROM f/u 1 yr	SWSL pre	SWLS Post	SWLS f/u 1yr	TBI model systems pre	TBI model systems f/u 1 yr
5201	follow up complete	YY	YY	YY	YY	YY	YY	YY	YY	YY
5202	treatment complete	n/a	YY	YY	n/a	YY	YY	n/a	YY	n/a
5203	treatment complete	n/a	YY	YY	n/a	YY	YY	n/a	YY	n/a
5204	treatment complete	n/a	YY	YY	n/a	YY	YY	n/a	YY	n/a
5205	treatment complete	n/a	YY	YY	n/a	YY	YY	n/a	YY	n/a
5206	treatment complete	n/a	YY	YY	n/a	YY	YY	n/a	YY	n/a
5207	treatment complete	n/a	YY	YY	n/a	YY	YY	n/a	YY	n/a
5208	treatment complete	n/a	YY	YY	n/a	YY	YY	n/a	YY	n/a
5211	treatment complete	n/a	YY	YY	n/a	YY	YY	n/a	YY	n/a
5212	follow up complete	YY	YY	YY	YY	YY	YY	YY	YY	YY
5213	treatment complete	n/a	YY	YY	n/a	YY	YY	n/a	YY	n/a
5214	treatment complete	n/a	YY	YY	n/a	YY	YY	n/a	YY	n/a
5215	treatment complete	n/a	YY	YY	n/a	YY	YY	n/a	YY	n/a
5217	treatment complete	n/a	YY	YY	n/a	YY	YY	n/a	YY	n/a
5218	treatment complete	n/a	YY	YY	n/a	YY	YY	n/a	YY	n/a
5219	treatment complete	n/a	YY	YY	n/a	YY	YY	n/a	YY	n/a
5222	treatment complete	n/a	YY	YY	n/a	YY	YY	n/a	YY	n/a
5227	treatment complete	n/a	YY	YY	n/a	YY	YY	n/a	YY	n/a
5228	Treatment complete	n/a	YY	YY	n/a	YY	YY	n/a	YY	n/a
5232	treatment complete	n/a	YY	YY	n/a	YY	YY	n/a	YY	n/a
5233	Treatment complete	n/a	YY	YY	n/a	YY	YY	n/a	YY	n/a
5237	treatment complete	n/a	YY	YY	n/a	YY	YY	n/a	YY	n/a
% Completed		9	100	100	9	100	100	9	100	9

Note. Our data quality assurance protocol dictates that the person who filled out the physical form should be the one to enter the data. Data in database is compared it to physical form by personnel from study other than the person who entered it.

Key to Codes in Table Cells. YY = data collected and entered; Y = data collected but not entered; . = data missing, i.e., data not collected; n/a = test date has not yet occurred.

Participant	status	WCST pre	WCST f/u 1 yr	WMS digit span pre	WMS digit span fu 1 yr	WMS log memory 1 pre	WMS log memory 1 f/u 1 yr	WMS log memory 2 pre
5201	follow up complete	YY	YY	YY	YY	YY	YY	YY
5202	treatment complete	YY	n/a	YY	n/a	YY	n/a	YY
5203	treatment complete	YY	n/a	YY	n/a	YY	n/a	YY
5204	treatment complete	YY	n/a	YY	n/a	YY	n/a	YY
5205	treatment complete	YY	n/a	YY	n/a	YY	n/a	YY
5206	treatment complete	YY	n/a	YY	n/a	YY	n/a	YY
5207	treatment complete	YY	n/a	YY	n/a	YY	n/a	YY
5208	treatment complete	YY	n/a	YY	n/a	YY	n/a	YY
5211	treatment complete	YY	n/a	YY	n/a	YY	n/a	YY
5212	follow up complete	YY	YY	YY	YY	YY	YY	YY
5213	treatment complete	YY	n/a	YY	n/a	YY	n/a	YY
5214	treatment complete	YY	n/a	YY	n/a	YY	n/a	YY
5215	treatment complete	YY	n/a	YY	n/a	YY	n/a	YY
5217	treatment complete	YY	n/a	YY	n/a	YY	n/a	YY
5218	treatment complete	YY	n/a	YY	n/a	YY	n/a	YY
5219	treatment complete	YY	n/a	YY	n/a	YY	n/a	YY
5222	treatment complete	YY	n/a	YY	n/a	YY	n/a	YY
5227	treatment complete	YY	n/a	YY	n/a	YY	n/a	YY
5228	Treatment complete	YY	n/a	YY	n/a	YY	n/a	YY
5232	treatment complete	YY	n/a	YY	n/a	YY	n/a	YY
5233	Treatment complete	YY	n/a	YY	n/a	YY	n/a	YY
5237	treatment complete	YY	n/a	YY	n/a	YY	n/a	YY
% Completed		100	9	100	9	100	9	100

Note. Our data quality assurance protocol dictates that the person who filled out the physical form should be the one to enter the data. Data in database is compared it to physical form by personnel from study other than the person who entered it.

Key to Codes in Table Cells. YY = data collected and entered; Y = data collected but not entered; . = data missing, i.e., data not collected; n/a = test date has not yet occurred.

Participant	status	WMS log memory 2 f/u 1 yr	WMS log memory recognition pre	WMS log memory recognition f/u 1 yr	WMS visual reproduction pre	WMS visual reproduciton f/u 1	fitness assesment pre	fitness assesment post	fitness assesment f/up 1 yr
5201	follow up complete	YY	YY	YY	YY	YY	YY	YY	Y
5202	treatment complete	n/a	YY	n/a	YY	n/a	YY	YY	n/a
5203	treatment complete	n/a	YY	n/a	YY	n/a	YY	YY	n/a
5204	treatment complete	n/a	YY	n/a	YY	n/a	YY	YY	n/a
5205	treatment complete	n/a	YY	n/a	YY	n/a	YY	YY	n/a
5206	treatment complete	n/a	YY	n/a	YY	n/a	YY	Y	n/a
5207	treatment complete	n/a	YY	n/a	YY	n/a	YY	YY	n/a
5208	treatment complete	n/a	YY	n/a	YY	n/a	YY	Y	n/a
5211	treatment complete	n/a	YY	n/a	YY	n/a	Y	Y	n/a
5212	follow up complete	YY	YY	YY	YY	YY	YY	YY	YY
5213	treatment complete	n/a	YY	n/a	YY	n/a	Y	Y	n/a
5214	treatment complete	n/a	YY	n/a	YY	n/a	Y	Y	n/a
5215	treatment complete	n/a	YY	n/a	YY	n/a	Y	Y	n/a
5217	treatment complete	n/a	YY	n/a	YY	n/a	Y	Y	n/a
5218	treatment complete	n/a	YY	n/a	YY	n/a	Y	Y	n/a
5219	treatment complete	n/a	YY	n/a	YY	n/a	Y	Y	n/a
5222	treatment complete	n/a	YY	n/a	YY	n/a	Y	Y	n/a
5227	treatment complete	n/a	YY	n/a	YY	n/a	Y	Y	n/a
5228	Treatment complete	n/a	YY	n/a	YY	n/a	YY	Y	n/a
5232	treatment complete	n/a	YY	n/a	YY	n/a	Y	Y	n/a
5233	Treatment complete	n/a	YY	n/a	YY	n/a	Y	Y	n/a
5237	treatment complete	n/a	YY	n/a	YY	n/a	Y	Y	n/a
% Completed		9	100	9	100	9	45	32	5

Note. Our data quality assurance protocol dictates that the person who filled out the physical form should be the one to enter the data. Data in database is compared it to physical form by personnel from study other than the person who entered it.

Key to Codes in Table Cells. YY = data collected and entered; Y = data collected but not entered; . = data missing, i.e., data not collected; n/a = test date has not yet occurred.

Participant	status	Pre scan Status	Post Scan Status	1 yr f/up scan status
5201	follow up complete	YY	YY	YY
5202	treatment complete	YY	YY	n/a
5203	treatment complete	.	.	.
5204	treatment complete	.	.	.
5205	treatment complete	.	.	.
5206	treatment complete	.	.	.
5207	treatment complete	.	.	.
5208	treatment complete	YY	YY	n/a
5211	treatment complete	.	.	.
5212	follow up complete	.	.	.
5213	treatment complete	.	.	.
5214	treatment complete	YY	YY	n/a
5215	treatment complete	.	.	.
5217	treatment complete	.	.	.
5218	treatment complete	YY	YY	n/a
5219	treatment complete	.	.	.
5222	treatment complete	.	.	.
5227	treatment complete	YY	YY	n/a
5228	Treatment complete	.	.	.
5232	treatment complete	.	.	.
5233	Treatment complete	.	.	.
5237	treatment complete	.	.	.
% Completed		27%	27%	.

Key to Codes in Table Cells. YY = data collected and entered; Y = data collected but not entered;
. = data missing, i.e., contraindication to MRI; n/a = test date has not yet occurred.